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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,708	04/02/2004	Wendy Lea Corbett	20892 US2	1192

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EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
08/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,708	CORBETT ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04/02/2004, 09/13/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :07/06/2004, 01/07/2005, 02/07/2005, 06/20/2005, 01/22/2007.

DETAILED ACTION

Application Status

1. Claims 1-4 are pending in this instant case.

Election

2. Applicant's election with traverse of Group II, (Claim 2) in the reply filed on 06/15/2007 is acknowledged. The traversal is on the ground(s) that the Office has not shown that a burden exists in searching the entire application, and the inventions are not independent or distinct. Applicants argue inventions are drawn to a crystal with ligands and without ligands, wherein both crystals having "the same unit cell dimensions and space group". Upon Applicants' argument and further consideration the previous restriction requirement is withdrawn.

Claim 1-4 will be examined herein.

Priority

3. Applicant's claim for the benefit of a divisional application of prior application 10/318308 filed on 12/12/2002 (now US Patent 6,911,545), which claims benefit of 30/341,988 filed on 12/19/2001 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

The application claims no priority for benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c).

Information Disclosure Statement

4. The information disclosure statements (IDSs) filed on 07/06/2004, 01/07/2005, 02/07/2005, 06/20/2005, 01/22/2007 have been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

The polypeptide in Figure 4 requires an appropriate SEQ ID NO. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.

The structural coordinates in Figure 4 teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

6. The specification is objected to because of the following informalities.

The Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the name of the source species (human liver isozyme) for completeness.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 recite the term "about" in the claims to describe the size of unit cell dimensions, concentration of protein or a molecule, or molecular weight of PEG, which makes claims unclear as to the metes and bounds it imparts on the claimed subject matter. For example, is the 5 mg/mL of glucokinase encompassed by the limitation of "about 9" Claim 3? Appropriate clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2 rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to any mammalian glucokinase crystals having a unit cell dimensions of a and b are from about 79 Å to about 80.2 Å; c is form about 318 Å to about 325 Å; α and β are 90°, γ is 120°; and the crystal has P6(5)22 space group

and the crystal has P6(5)22 symmetry; and method of making said crystals providing any mammalian glucokinase, adding any ligands, and growing crystal using a very widely varying buffer compositions of about 16% to about 25% PEG, about 0 to about 30% w/v glucose and about 8 to about 10 mM DTT.

While the structure and function of one species of said genera of mammalian glucokinase are disclosed in the specification, the common structural characteristics of species that define said genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

Instant specification describes a crystallization of (one of two isoenzyme) human glucokinase in liver with or without the presence of ligands. While the specification describes species of crystals that falls within the instant claimed genera of crystal, the breadth of claims encompassed by Claims 1 and 2 are so broad as to encompass any mammalian glucokinase crystal with or without any ligand(s) having unit cell dimensions of "a and b are from about 79 Å to about 80.2 Å; c is form about 318 Å to about 325 Å; α and β are 90°, γ is 120°; and the crystal has P6(5)22 space group"; wherein claimed mammalian glucokinase encompasses very widely varying polypeptide sequence and very widely varying unit cell dimensions. The protein crystals described by Figure 1 and 3 are within the genera of Claim 1-2 based on their space group symmetry, unit cell dimensions.

While the claim language requires a function for the instant genera of crystals (that of human glucokinase), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant genera as a whole. In general, for a species of crystal to be adequately structurally described, the following must be adequately disclosed: (1) the composition of the crystal [exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it], (2) the space group, and (3) the unit cell dimensions of the crystal. The disclosed instant species of crystals have not adequately met this burden by the description in the instant specification. Specifically, the composition of the crystals encompassed by the breadth of the claims is not described because the exact molecule is not limited, nor the

space group (in view of the term "about" which makes the range of limitation unclear) and unit cell dimensions associated with this breadth of chemical composition described. In Claims 1 and 2, only unit cell dimensions and space group are adequately described and these recited unit cell dimensions and space group cannot describe any mammalian glucokinase crystal encompassed by the claims. The exact polypeptide sequence of SEQ ID NO: 1 is not identified or disclosed in the claim. The space group disclosed in Claim 2 satisfies one adequate description but missing the other two description as noted above because the recited unit cell dimensions in range accompanied by the term "about" does not meet the requirement above adequately. A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the disclosed species of the instant disclosure. While the structure and function of one species of said genera of mammalian glucokinase are disclosed in the specification, the common structural characteristics of species that define said genera are not described. Claims drawn to the instant genera of crystals are also not adequately described. Therefore, one skilled in the relevant art would be unable to make and use the claimed invention by virtue of the instant disclosure from the specification.

9. Claims 1-4 rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method for preparing protein crystals of a polypeptide consisting SEQ ID NO: 1 (GST-GK fusion protein) by crystallizing said polypeptide with ligands disclosed in Examples 3-10, or without ligands (Example 2), that results in a crystal having the space group P6(5)22 and the unit cell dimensions within the range recited in Claims 1 and 2, does not reasonably provide enablement for all crystals and methods of preparation thereof as broadly encompassed by the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The breadth of the claims: Claims 1 and 2 are so broad as to encompass any mammalian glucokinase crystal with or without any ligand(s) having unit cell dimensions of "a and b are from about 79 Å to about 80.2 Å; c is form about 318 Å to about 325 Å; α and β are 90°, γ is 120°; and the crystal has P6(5)22 space group"; wherein claimed mammalian glucokinase encompasses very widely varying polypeptide sequence and very widely varying unit cell dimensions. Claims 3 and 4 are drawn to a process for crystallizing any mammalian glucokinase in the presence of any allosteric ligand in a widely varying reservoir solution recited in Claim 3 in view of the term "about", which makes the scope of limitation unclear.

The nature of the invention: The invention is related to protein crystals of human liver glucokinase isoenzyme fused with GST (SEQ ID NO: 1) and method of crystallizing thereof. At the time of the invention, protein crystallization was well known in the art. However, the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Regarding the claimed crystals, the state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (2001, *Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., which teaches that the formation of protein crystals is critically

dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, *e.g.*, pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Along these same lines, Wiencek (*Ann Rev Biomed Eng,* 1999, 1:505-534) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of any other mammalian glucokinase, with or without any ligand, can be achieved using the crystallization parameters as set forth at p. 43-48 of the specification. Furthermore, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of SEQ ID NO: 1 or any other protein encompassed by Claim 1 and 2 can be achieved using a claimed genus method of crystallization parameters as described Claims 3 and 4, with or without any ligand; and impossible to predict by one skilled in the art because a crystal that diffract to give a good resolution must be determined by X-ray crystallography. The exact crystallization method with or without ligands in Claims, accompanied by the word "comprises" does not disclose the exact composition used in method steps for the crystallization protein crystals in Claims 3 and 4.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses several working example of the claimed crystal

and the method of crystallization thereof. See specification at pp. 43-48. Other than these working examples, the specification fails to provide guidance for altering the crystallization conditions for crystallizing any mammalian glucokinase with or without any ligands with an expectation of obtaining diffraction-quality crystals.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, these methods are specific to a particular protein as evidenced by the above teachings. Thus, a skilled artisan is left to experiment by a trial and error process to determine whether the claimed crystallization conditions can be applied to crystallization of other mamalian glucokinase with or without any ligands; or whether residues SEQ ID NO: 1 can be crystallized under a different set of crystallization parameters which encompass the wide range of crystallization condition.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with

the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, preparation of any crystal encompassed in Claim 2 with desired characteristics of unit cell dimensions and space group is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Aleshin et al. (2000, Mar. 3, J. Mol. Biol, volume 296, pages 1001-1015).

Claims 3 and 4 are drawn to a process for crystallization comprising: providing a mammalian glucokinase, adding a molar excess of the allosteric ligand, and growing crystals by vapor diffusion by the buffer having components recited in Claim 4.

Aleshin et al. teach a crystallization of human hexokinase, which is one of glucokinase (GK), in the presence of "1 mM Glc", which is encompassed by an allosteric ligand, and the crystal were "growing by the hanging drop" which involves a vapor diffusion process. The broad and reasonable interpretation of recited limitations

regarding a concentration of the GK, PEG, glucose, DTT or the molecular weight of PEG has been given in view of the term "about". Thus, said concentration limitations are met by the method of Aleshin et al. using 20 mg/ml GK (page 1012, line 16), 20% PEG 8000, 1 mM DTT (middle of page 1012, middle) as described in "Crystal preparation" in page 1011-1012.

The streaking of the mammalian GK solution with ligand and streaking the reservoir solution across the droplet of protein solution is met by the step of Aleshin et al. disclosing a mixing a precipitant solution with the GK solution for hanging drop. This mixture would have shape of X when two solutions are mixed in such way. Thus, the method of Aleshin et al. meets the limitations of Claims 3 and 4.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
August 13, 2007

KATHLEEN KERR BRAGDON, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10/816,708	Applicant(s) Corbett et al.	
	Examiner Alexander Kim	Art Unit 1656	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See next page.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
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PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

7. cont.

The polypeptide in Figure 4 require an appropriate SEQ ID NO. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.

The structural coordinates in Figure 4 teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.